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## Final Report

## "Dynamic Biophysical Theory for the Role of Hippocampal Neural Networks in the Declarative Memory System"
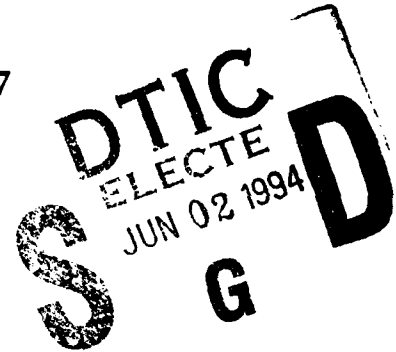
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This grant was awarded to support collaborative work between our laboratory and the laboratory of Prof. Tom Brown at the Dept. of Psychology at Yale University. The principal theme of the research we carried out relates to understanding the biophysics of learning at the level of dendrites and spines. It relates to an area of research we term "Biophysics of Computation". What are the biophysical mechanisms at the cellular or sub-cellular level that implement the elementary neuronal operations underlying information processing and storage? What are the elementary units of information processing, the diodes and transistors of the brain? Properties and limitations of neurons and synapses are crucial in determining the algorithms used to perform specific computational tasks. This applies in particular to the function of dendritic spines and their key involvement in plasticity.

Dendritic spines, small protrusions covering the surface of many neurons, have fascinated anatomists ever since Ramon y Cajal first described them at the turn of the century. Experimental and computational studies now seem to be converging towards a common viewpoint of spines as providing biochemical, rather than electrical, compartmentalization within neurons. Spines are numerous. As many as 15,000 spines, at a density of 2 spines per micrometer of dendritic length, cover the surface of a layer V pyramidal cell in the visual cortex. Spines are the major postsynaptic target of excitatory (asymmetric, type I) synaptic input. Spines are also tiny. Their precise

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morphology has been revealed by the 3-D EM reconstructions of cortical pyramidal cells. Necks range in length from 0.08-1.58 μm and in diameter from 0.04-0.46 μm. Spines are so small that at a resting calcium concentration of 80 nM only about three (yes, 3) free calcium ions are expected to be found in an averaged sized spine head.

The shape of dendritic spines, in particular the length and diameter of the spine neck, can change during neuronal development or in response to some behaviorally significant stimuli (such as light, social interaction, motor activity). High-frequency electrical stimulation of specific hippocampal pathways—sufficient to induce long-term potentiation (LTP)—have also been reported to alter spine morphology, leading to larger spine heads, changes in the shape of the spine stem, an increased incidence of concave spine heads and an increase in the number of shaft synapses. However, it is unclear what direct role, if any, these changes have in the increase in synaptic efficiency.

What functional role might spines play? Because dendritic spines are so closely associated with excitatory synaptic traffic, they seem ideally suited to modulate information processing in the brain. Thus, they have been subject to analysis by theoreticians. Rall first argued that the spine neck offers a significant resistance to the electrical charge flowing from the synapse on the spine head to the dendrite and, ultimately, to the cell body. Thus, changing the morphology of the spine neck can lead to significant changes in the somatic excitatory postsynaptic potential (EPSP), providing a possible anatomical substrate for long-term memory. This basic insight was refined and extended by Koch and Poggio (1983, 1984), showing that for fast synaptic inputs the critical factor in determining the spine's electrical behavior is the ratio $g_{syn}/g_{neck}$, the synaptic-induced conductance increase at the spine head divided by the spine axial (neck) conductance. If this ratio is small, the synaptic stimulus does not change the membrane potential much and so behaves as a current source. Thus, changing the spine dimensions cannot provide a mechanism for potentiation. On the other hand, if $g_{syn}$ is large compared to $g_{neck}$, the EPSP in the spine will approach the synaptic reversal potential, and the synaptic stimulus behaves as a fixed voltage source. In this case, increasing the spine neck resistance by stretching the spine stem or by reducing its diameter reduces the dendritic EPSP.

Experimental estimates of the fast (AMPA) component of $g_{syn}$ from hippocampal slice and culture preparations range from about 0.05-0.5 nS (Brown *et al.* 1991). Values of $g_{neck}$ inferred from spine morphology fall between 18-138 nS. Therefore, widening or shortening the spine neck will have little influence on the voltage attenuation properties of the spine.

It is known that the induction of LTP at some synapses requires a *postsynaptic increase in intracellular calcium concentration; this increase is*

thought to be mediated by calcium influx through the NMDA receptor complex. Thus, computer models---using either voltage-dependent calcium or NMDA channels---have increasingly focused on the role of spines in modulating calcium dynamics following synaptic input (Gamble and Koch, 1987; Zador, Koch and Brown, 1991).

Because of the similarity in the underlying equations, insights obtained from the analysis of membrane potential can be applied to the analysis of calcium dynamics. For instance, due to the small and highly restricted volume of the spine, a small calcium influx following synaptic stimulation causes a large, transient increase in the calcium concentration within the spine. The resulting increase in calcium will be much smaller, however, at the dendrite, since it's large volume acts as a sink for the calcium ions diffusing from the spine head down the neck. Thus, the calcium attenuation between the spine head and base is expected to be large (Koch and Zador, 1993). Furthermore, if the dendritic calcium concentration is ``clamped" to 1 $\mu$M, the spine head can be protected from the high dendritic calcium concentration by the presence of standard densities of calcium pumps in the membrane of the spine neck (Koch, Zador and Brown, 1992).

Some of these properties have now been visualized by using the fluorescent calcium indicator dye fura-2 in the hippocampal slice (Müller and Connor, 1991; Guthrie, Segal and Kater, 1991). In particular, Guthrie and colleagues visualize calcium gradients following a sustained rise in intracellular calcium (to 0.2-1.5 $\mu$M levels) caused by controllable photo-induced damage. In a subset of the spines, changes in spine calcium lag substantially behind the rise in dendritic calcium. Control experiments with injected cobalt suggest that no physical diffusion barrier exists between the dendrite and the spine, supporting the idea that calcium-dependent processes, such as calcium pumps or other uptake systems, are responsible for isolating the spine head. This property would also explain why elevated calcium levels in the dendrite in the absence of synaptic stimuli to the spines fail to induce LTP at those spines (Koch and Zador, 1993).

Thus, both experimentalists and theoreticians are shifting their viewpoint from seeing spines as devices that modulate electrical properties towards a view of spines as devices subserving chemical compartmentalization. One of the key functions of spines, then, would be to amplify and isolate the synaptically induced calcium, or any other second messenger, within individual spines. In other words, dendritic spines would be crucial for the induction of information storage in the brain, rather than for its retention.

**Publications Directly Resulting From this Grant**

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